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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/591,632	06/09/2000	Susan Lindquist	27373/34978A	2820

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EXAMINER	
TURNER, SHARON L	
ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 08/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/591,632	LINDQUIST ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65,67,81,101-110,116-119 and 121-149* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *121-123,139 and 144* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *65,67,81,101-110,116-119 and 121-149* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 65,67,81,101-110,116-119,124-138,140-143 and 145-149.

Response to Amendment

1. The Examiner and/or Art Unit of U.S. Patent application SN 09/591,632 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Examiner Turner, Technology Center 1600, Art Unit 1649.

2. The amendment filed 5-9-05 has been entered into the record and has been fully considered.

3. Claims 65, 67, 81, 101-110, 116-119, 121-149 are pending.

4. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

5. As a result of Applicants amendment, all rejections not reiterated herein have been withdrawn by the Examiner.

Election/Restrictions

6. Applicant's election with traverse of Group VII, claims 121-123, 139 and 144 and peptide of SEQ ID NO:2, particularly residues of NM regions (1-253), N region (1-123) and substitution of cysteine residue in the reply filed on 5-9-05 is acknowledged. The traversal is on the ground(s) that there is no substantial burden (pp. 12-13 of response), no search burden with respect to SEQ ID NO:2 and substitutions (pp. 13-14), that there was a failure to identify characteristics that define the restriction groups (p. 14), that the restriction of fiber/polymer claims was improper (pp. 14-15), that the restriction of polypeptides was improper (p. 15-16) and that the restriction to delineate the molecular embodiments is improper (p. 16-17). This is not found persuasive because the search

burden with respect to each of the newly delineated products is substantial. The delineated products were newly amended as presented in the 7-19-04 submission, thereby necessitating the 2-7-05 restriction. These claims were not previously searched and or considered on the merits by the previous Examiner during the course of examination. In contrast to Applicant's assertion, the record is clear that the previous search and examination based upon previous restriction was limited to the extent of SEQ ID NO:2 and cysteine substitutions, see action of 1-13-04, page 2, third paragraph.

The newly recited products are patentably distinct and distinguished as separately claimed. They differ in amino acid composition and in higher order structures as set forth in several independent and dependent claims drawn to various forms of "filamentous polymers", "fibrous polymers", "fibers", and distinct "polypeptides". The prosecution history is noted. However, no claims are instantly deemed to be allowable. Moreover, as set forth in the restriction requirement, the restriction was instituted in part upon Applicants assertion of patentability of particular higher order structures. Applicants reference to a SCHAG amino acid sequence is noted. However, as delineated in the specification, the SCHAG amino acid sequence is variable in amino acid sequence and in higher order structures that may be formed. It is common practice within the PTO that polypeptide sequences may be restricted one from another as they each comprise different non-coextensive searches. It is not clear that any polypeptides share each of the higher order composites as separately claimed. The claims remain drawn to separate non-coextensive generic or sub-generic recitations and the relationships amongst the different sets are not set forth.

Neither have Applicants stated that the different claim sets are not patentably distinct nor is it clear that a reference to any one structure would constitute a reference to any other. Restriction is therefore maintained until evidence of allowability or admission on the part of Applicants that the claims are not patentably distinct in which case a reference to one species may be suitably used against another. The Examiner does further note different classification of higher order product structures, specifically to various polymers, fibers, and filaments, further evidencing the basis for restriction. To the extent that the products are not evidenced to be the "same", restriction therefore is maintained. It is further noted that previous arguments on the record with respect to cited art indicate Applicants belief that particular higher ordered peptide structures are patentable over the same products which are in different aggregate "form". Indeed the previous Examiner removed prior art rejections upon such argument by Applicants. Accordingly, restriction is maintained until the indication of allowable subject matter or until resolution over the issue of patentable "distinctness" amongst the various structural compositions. It is noted that the elected invention as delineated includes recitations to "polypeptides" and to "fibrous polymers" and are examined to the exent distinguished via the claims. Resolution of these issues and "finality" of the restriction requirement is deferred until such time that the Examiner has reviewed Applicant's response to the instant Office Action. The requirement is still deemed proper and is therefore maintained.

7. Claims 65, 67, 81, 101-110, 116-119, 124-138, 140-143,145-149 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected

invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5-9-05. Claims 121-123, 139, and 144 are under examination.

Claim Objections

8. Claim 144 is objected to because of the following informalities: The claims recites a substituted amino acid selected from "glutamate" and "aspartate". The art standard term for these amino acids is generally Glutamic Acid and Aspartic Acid, abbreviated in the literature as "Glu", or "E" and "Asp" or "D" in reference to amino acid sequences. Appropriate correction is required.

Priority

9. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 121-123, 139 and 144 of this application. The claims differ substantially from that disclosed within the provisional and

originally filed specification. In particular the peptides of claims 121-123and 144 differ in composition and further the "fibrous polymer" newly recited is not apparently disclosed. Accordingly, the effective filing date awarded for the purposes of examination is that of instant filing date 6-9-00. Traversal should delineate where support may be found for instant recitations within the specification as originally filed and within the provisisonal.***Claim Rejections - 35 USC § 112***

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 121-123, 139 and 144 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The claims as amended differ substantially from those originally filed. Moreover, the claims newly delineate a "fibrous polymer" which recitations are not apparently supported as claimed. Support for the recitations of the claims should be provided from the specification as originally filed.

12. Claims 121-123, 139 and 144 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification describes various polypeptide sequences consisting of Sup35 and Ure2 amongst specific chimeric constructs for example which are disclosed as capable of aggregating as analyzed via spectroscopy or electron micrographs, see for example pp. 44-92. The specification also refers to a "SCHAG amino acid sequence" inclusive of a nearly unlimited number of multiple different amino acid compositions and various aggregate structures as contemplated throughout pp. 6-12 of the specification. The claims as written recite various polypeptides, polypeptide fragments and higher order structures of "fibrous polymers" comprising fragments of substituted amino acids that "self-coalesce" into "higher order aggregates". These recitations encompass various fragments, portions and aggregates that are of nearly unlimited structural breadth. Yet, the specification is limited to experimentation with only particular Sup35/URE2 variants and analysis via spectroscopy and electron micrographs. The instant disclosure of particular polypeptides analyzed for second order characteristics via binding or aggregation with spectroscopy or EM, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc.,

107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification however, fails to delineate the structural constraints of a "fibrous polymer" and fails to distinguish those amino acids and conditions required to form them. Further, the specification fails to delineate the structural constraints and conditions whereby various different aggregate structures may be formed. Protein aggregation is dependent upon multiple conditions inclusive of the amino acid sequence of the peptides, pH, temperature, salt concentration, the presence of alternative peptides, cell membranes and other

components that are of nearly unlimited breadth. Such is extensively exemplified throughout the IDS. For example, IDS C12 Dagkesamanskaia teaches differential effect of fusion of glutathione S-transferase on aggregation of yeast Sup35 protein. IDS C15 DePace notes critical roles for amino-terminal Glutamine/Asparagine repeats in yeast prion aggregation. IDS C56 Glover notes the ability of various Hsp proteins to abrogate aggregation. IDS C64 Jackson notes various conditions (oxidation/reduction etc) that affect prion (aggregate) formation. Accordingly, the description provided is insufficient to teach the conditions and structural constraints required whereby suitable "fibrous polymers" and/or "higher ordered aggregates" may be formed.

13. Claims 121-123, 139 and 144 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for aggregation as analyzed via spectroscopy and EM as exemplified throughout pp. 44-92 of the specification, see in particular experimentation with Sup35/URE2, does not reasonably provide enablement for the formation of fibrous polymers or for the scope of the polypeptides and fragments encompassed as directed to substituted amino acids and fragments of substituted amino acids such that they self-coalesce to form "fibrous polymers" or higher ordered aggregates". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working

examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

Applicants claims are directed to peptides and partial peptides with greater than single amino acid substitutions and which have the property of self-coalescing to form higher ordered aggregates or fibrous polymers. However, the specification does not teach the experimental variables amongst different experimental conditions and amino acid sequences that determine higher ordered aggregate structure or formation of fibrous polymer formation.

The specification does not enable the broad scope of the claims that encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that requisite structure is maintained. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful in any particular form and the skilled artisan would not expect similar structure amongst different sequences or different experimental conditions. For example, the artisan recognizes that protein aggregation is dependent upon multiple conditions inclusive of the amino acid sequence of the peptides, pH, temperature, salt concentration, the presence of alternative peptides, cell membranes and other components that are of nearly unlimited breadth. Such is extensively exemplified throughout the IDS. For example, IDS C12 Dagkesamanskaia teaches differential effect of fusion of glutathione S-transferase on aggregation of yeast Sup35 protein. IDS C15 DePace notes critical roles for amino-terminal Glutamine/Asparagine repeats in yeast prion aggregation. IDS C56 Glover

notes the ability of various Hsp proteins to abrogate aggregation. IDS C64 Jackson notes various conditions (oxidation/reduction etc) which affect prion (aggregate) formation. Secondary structure is dependent and variable upon such factors. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims. Further as to the terms "self-coalesce", "higher ordered aggregates" and "fibrous polymers" the skilled artisan is not provided with a recognized structural conformation or suitable conditions whereby any amino acid construct or composition may be assessed for assembly as required.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed polypeptides and fibrous polymers without further undue experimentation.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 121-123, 139 and 144 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "higher ordered aggregates" in the claims and the term "fibrous polymer" in claim 139 are relative terms which render the claims indefinite. The terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Accordingly, it is further noted that claims 121-123 and 139 do not necessarily appear to further limit claim 144.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 121-123, 139 and 144 are rejected under 35 U.S.C. 102(b) as being anticipated by Wei et al., J. of Biol. Chem., 273(19):11806-814, 1998 as evidenced by Levy et al., J. Exp. Med., 169:1771-78, May 1989.

The claims are inclusively directed to polypeptide fragments that comprise substitutions of cysteine, lysine, tyrosine, glutamic acid, aspartic acid and arginine and that self-coalesce to form higher ordered aggregates. Cystatin C aggregates are suitable to form higher ordered aggregates that comprise fibrous polymers or fibrils in patients with HCHWA-I, see in particular Abstract and col. 1-2, p. 11806. The amino acid sequence of Cystatin C is evidenced by Levy et al., 1989. The polypeptides of the claims relate to single amino acid substituions. Any of the residues of Cystatin C either in the variant or wild type form that are of cysteine, lysine, tyrosine, glutamic acid,

aspartic acid or arginine are sufficient to qualify as polypeptides comprising suitable portions or fragments that form higher ordered aggregate and fibrous polymer structures as the peptides are noted to form amyloid fibrils. All residues are exposed to the environment. Thus, Wei as evidenced by Levy fairly teach the invention.

18. Claims 121-123, 139 and 144 are rejected under 35 U.S.C. 102(b) as being anticipated by Kushnirov et al., Yeast, 6:461-472, 1990 IDS C76.

The claims are inclusively directed to polypeptide fragments that comprise substitutions of cysteine, lysine, tyrosine, glutamic acid, aspartic acid and arginine and that self-coalesce to form higher ordered aggregates. The claims also refer to peptides of SEQ ID NO:2 with substitution at residue 184. Residue 184 is K, lysine, and is in the context of the amino acid sequence "TKE". Kushnirov teach both divergence and conservation of SUP2 (SUP35) gene of yeast Pichia pinus and Saccharomyces cerevisiae. Mutation of the lysine residue to glutamate/glutamic acid results in the sequence "TEE" found in Pichia pinus SUP2/SUP35 at residues 215-217. The Pichia variant thus comprises a suitable substitution fragment where the substitution is glutamate/glutamic acid. All residues are exposed to the environment. Kushnirov is silent as to the aggregating properties. However, it is noted that the peptide is significantly homologous (60.6%) to the cerevisiae protein. A peptide and its properties cannot be separated. To the extent that the structural constraints of the peptides are fairly met, the properties of forming higher ordered aggregates and fibrous polymers are deemed inherent absent convincing factual evidence to the contrary. The PTO has

insufficient resources to test the Kushnirov peptide for its aggregating properties. Thus the reference teachings anticipate the claimed invention.

Conclusion

19. No claims are allowed.

20. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Thursday from 7:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at (571) 272-0867.

Sharon L. Turner, Ph.D.
July 19, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
7/19-05